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EXAMINER
HUYNH, PHUONG N

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/761,636	Applicant(s) ACHEN ET AL.	
	Examiner " Neon" Phuong Huynh	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 April 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,12-18,23-26 and 49-63* is/are pending in the application.

4a) Of the above claim(s) *4, 14-17, 25, 52, and 56-62* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,12,13,18,23,24,26,49-55 and 63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 1-4, 12-18, 23-26 and 49-63 are pending.

2. Applicant's election with traverse of Group I, Claims 1-3, 12-13, 18, 23-24, 26, 49-55 and 63, drawn to a monomeric monocyclic peptide and composition comprising said monomeric monocyclic peptide that read on the species comprising cyclic peptide No. 2 as identified in Table 1 on page 32 of specification which corresponds to SEQ ID NO: 6, filed 4/24/02, is acknowledged. The traversal is on the grounds that (1) the monomeric peptide of Group I and the dimeric bicyclic peptide of Group II are related, (2) the monomer and dimmer are related since the claimed dimmer actually comprise the claimed monomers. This is not found persuasive because dimeric bicyclic peptide includes homodimeric and heterodimeric peptides which consisting of two different monomeric peptide. Further monomeric monocyclic and dimeric bicyclic peptides differ with respect to their structure and physiochemical properties for the reasons set forth in the restriction mailed 3/26/02. Finally, a prior art search also requires a literature search. It is a burden to search more than one invention. Upon reconsideration, the prior art search has been extended to species of cyclic peptides of SEQ ID NOS: 5, 7 and 10-14. Therefore, the requirement of Group I (now claims 1-3, 12-13, 18, 23-24, 26, 49-55 and 63) and Groups II-XII is still deemed proper and is therefore made FINAL.

3. Claims 4, 14-17, 25, 52, and 56-62 are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

4. Claims 1-3, 12-13, 18, 23-24, 26, 49-55 and 63 drawn to a monomeric monocyclic peptide and composition comprising said monomeric monocyclic peptide that read on the species comprising cyclic peptides of SEQ ID NO: 5-7, 10-14 are being acted upon in this Office Action.

5. The drawings, filed 1/18/01, are not approved. Please see enclosed PTO 948, Notice of Draftsperson's Patent Drawing Review. Appropriate action is required.

6. Claim 12 is objected to because it depends on non-elected claim 5.

7. Claim 18 is objected to because it depends on non-elected claims 10 and 5.

8. The disclosure is objected to because of the following informality: incorporation of subject matter into the patent application by reference to a hyperlink and/or other forms of browser-executable code is considered to be an improper incorporation by reference. See MPEP 608.01(p), paragraph I regarding incorporation by reference. Therefore the embedded hyperlinks and/or other forms of browser-executable code disclosed on pages 29, line 25 of the instant specification are impermissible and require deletion. Where the hyperlinks and/or other forms of browser-executable codes are part of applicant's invention and are necessary to be included in the patent application in order to comply with the requirements of 35 U.S.C. 112, first paragraph, and applicant does not intend to have these hyperlinks be active links, then this objection will be withdrawn and the Office will disable these hyperlinks when preparing the patent text to be loaded onto the PTO web database. Appropriate action is required.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-3, 12-13, 18, 23-24, 26, 49-55 and 63 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) a monomeric monocyclic peptide selected from the group consisting of SEQ ID NO: 5, 6 and 7 which interferes with cell survival of at least one factor selected from the group consisting of VEGF, VEGF-C, and VEGF-D mediated by at least one receptor selected form the group consisting of VEGF receptor-2 and VEGF receptor-3, (2) a monomeric monocyclic peptide selected from the group consisting of SEQ ID NO: 5, 6 and 7 which interferes with cell survival of at least one factor selected from the group consisting of VEGF mediated by at least one receptor selected form the group consisting of VEGF receptor-2 and VEGF receptor-2, (3) a monomeric monocyclic peptide selected from the group consisting of SEQ ID NO: 5, 6 and 7 which interferes with cell survival of at least one factor selected from the group consisting of VEGF mediated by at least one receptor selected form the group consisting of VEGF receptor-2 and VEGF receptor-3, (4) a monomeric, monocyclic peptide selected from the group consisting of SEQ ID NOS: 5, 6 and 7 produced by a method comprising obtaining a peptide loop fragment from an exposed loop of a growth factor

protein or a corresponding loop fragment with one or more amino acid substitutions; measuring beta-beta carbon separation distances on opposing antiparallel strands of the loop fragment; selecting a beta-beta carbon location with a separation distance less than 6 angstroms; providing a cysteine residue in each opposing antiparallel strand at the selected beta-beta location and cyclizing the peptide by oxidizing the provided cysteine residues to form a disulfide bridge between strands, (5) a monomeric monocyclic peptide selected from the group consisting of SEQ ID NOS: 5, 6 and 7 which interferences with cell survival of at least one factor selected from the group consisting of VEGF, VEGF-C, and VEGF-D mediated by at least one receptor selected form the group consisting of VEGF receptor-2 and VEGF receptor-3 for inhibition of VEGF, VEGF-C, and VEGF-D mediated cell survival *in vitro*, **does not** reasonably provide enablement for (1) *any* monomeric monocyclic peptide which interferes with *any* biological activity of at least one factor selected from the group consisting of VEGF, VEGF-C, and VEGF-D mediated by at least one receptor selected from the group consisting of VEGF receptor-2 and VEGF receptor-3, (2) *any* monomeric monocyclic peptide mentioned above which interferes with *any* biological activity of at least one factor selected from the group consisting of VEGF, VEGF-C, and VEGF-D mediated by at least one receptor selected from the group consisting of VEGF receptor-2, (3) *any* monomeric monocyclic peptide mentioned above which interferes with *any* biological activity of at least one factor selected from the group consisting of VEGF, VEGF-C, and VEGF-D mediated by at least one receptor selected from the group consisting of VEGF receptor-3, (4) *any* monomeric monocyclic peptide produced by *any* method of making a monomeric monocyclic peptide as recited in claim 5, (5) *any* monomeric monocyclic peptide produced by *any* method of making a monomeric monocyclic peptide as recited in claim 5 which interferes with *any* biological activity of at least one factor selected from the group consisting of VEGF, VEGF-C, and VEGF-D mediated by at least one receptor selected from the group consisting of VEGF receptor-2 and VEGF receptor-3, (6) *any* cyclic peptide produced according to the method mentioned above further comprising deleting *any* one or two internal amino acid residues from said loop fragment prior to cyclizing the peptide, (7) *any* composition of matter comprising *any* monomeric monocyclic peptide mentioned above and at least one pharmaceutical carrier or adjuvant, (8) *any* composition of matter comprising *any* monomeric peptide produced by the method mentioned above and at least one pharmaceutical carrier or adjuvant, (9) *any* composition of matter comprising *any* monomeric monocyclic peptide mentioned above further comprising deleting *any* one or two internal amino acid residues from said loop fragment prior to cyclizing

the peptide, and at least one pharmaceutical carrier or adjuvant, and (10) *any* cyclic peptide "comprising" a peptide sequence such as the ones recited in claim 49, wherein the peptide is a monomeric monocyclic peptide which interferes with any biological activity mediated by at least one receptor selected from the group consisting of VEGF receptor-2, VEGRF receptor-3, (11) *any* cyclic peptide comprising SEQ ID NO: 5, SEQ ID NO: 6, (12) *any* cyclic peptide mentioned above which interferes the activity of VEGF-D and/or VEGF-C but not VEGF, mediated by VEGF receptor-2 for treating *any* disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only various monomeric monocyclic peptides such as the ones shown in Table 1 on page 32 and Table 2 on page 47 of the specification. However, only three monocyclic peptides (peptides number 1-3), which correspond to SEQ ID NO: 5, 6, 7, respectively, have been demonstrated to inhibit VEGF-DΔNΔC, VEGF-C, VEGF-D and mouse VEGF164 induced VEGFR-2 and VEGFR-3 mediated cell survival *in vitro*. Note, none of the monocyclic peptides shown in Table 2 and dimeric bicyclic peptides shown in Table 3 were found to inhibit *any* VEGF, VEGF-DΔNΔC, VEGF-C, VEGF-D and mouse VEGF164 induced VEGFR-2 and VEGFR-3 mediated cell survival *in vitro*. The specification further discloses that heterodimeric bicyclic peptide number 5, which corresponds to SEQ ID NO: 8 linked to SEQ ID NO: 9 (Table 1 on page 32) caused a significant reduction in cell number (Fig 11b). In contrast, neither homodimeric bicyclic peptides 4 and 6, which correspond to SEQ ID NO: 8 linked to SEQ ID NO: 8 or SEQ ID NO: 9 linked to SEQ ID NO: 9 caused a significant change in cell number (page 39). None of the dimeric bicyclic peptides mentioned above appear to be more effective inhibitors than the monomeric monocyclic peptides in VEGF-D induced VEGFR-3 cell survival. The specification also discloses that deletion mutant selected from the group consisting

of SEQ ID NO: 10, 11 and 12 having one or two internal amino acid deletion or amino acid substitution fail to inhibit the VEGF-DΔNΔC, VEGF-C, VEGF-D and mouse VEGF164 induced VEGFR-2 and VEGFR-3 mediated cell survival *in vitro*.

Other than the specific monomeric monocyclic peptides mentioned above for inhibiting the VEGF mediated cell survival *in vitro*, the specification does not teach how to make and use *any* (1) monomeric monocyclic peptide mentioned above which interferes with *any* biological activity of at least one factor selected from the group consisting of VEGF, VEGF-C, and VEGF-D mediated by at least one receptor selected form the group consisting of VEGF receptor-2 and VEGF receptor-3 for *any* composition comprising *any* undisclosed monomeric monocyclic peptides for treating *any* disease. Without the specific amino acid residues or SEQ ID NO, there is no structure associated with the phrase "monomeric monocyclic peptide". Given the indefinite number of undisclosed peptide as long as it is monocyclic, there is insufficient guidance and working examples as to the structure associated with functional properties, in turn, would be useful for inhibiting VEGF-DΔNΔC, VEGF-C, VEGF-D and mouse VEGF164 induced VEGFR-2 and VEGFR-3 mediated cell survival in vitro, in turn, would be useful for treating any disease in vivo. As shown in Table 2 of the specification, not all monomeric monocyclic peptides are created equal and demonstrate to have the desired inhibitory activity. Even the specific amino acid residues are disclosed as shown in Table 2, it is unpredictable which monomeric monocyclic peptides would be useful for inhibiting VEGF VEGF-DΔNΔC, VEGF-C, VEGF-D and mouse VEGF164 induced VEGFR-2 and VEGFR-3 mediated cell survival in vitro, in turn, would be useful for inhibiting VEGF mediated cell survival in vivo. Further, there is no in vivo data in the specification as filed to support that any monomeric monocyclic peptides mentioned above would inhibit the VEGF meditated cell growth (survival).

Attwood *et al* teach that protein function is context-dependent and the state of the art of making functional assignments merely on the basis of some degree of similarity between sequences and the current structure prediction methods is unreliable. Skolnick *et al* teach that squence-based methods for function prediction are inadequate and knowing a protein's structure does not necessary tell one it's function (See entire document, Abstract in particular). Without the specific amino acid sequence, and given the indefinite number of monomeric monocyclic peptides, it is unpredictable which undisclosed monomeric monocyclic peptides would be effective as an inhibitor of VEGF mediated biological activity for treating any disease such as cancer in a patient. A pharmaceutical composition in the absence of in vivo data are

unpredictable for the following reasons: (1) the monomeric monocyclic peptide may be inactivated before producing an effect, i.e. such as proteolytic degradation or short half-lives; (2) the monomeric monocyclic peptide may not reach the target area because, i.e. the monomeric monocyclic peptide may not be able to stay long enough in circulation due to clearance or simply has no effect; and (3) other functional properties, known or unknown, may make the monomeric monocyclic peptide unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992). Given the undisclosed monomeric monocyclic peptides mentioned above are not enabled, it follows that any composition comprising said monomeric monocyclic peptides are not enabled.

With regard to a cyclic peptide "comprising" a peptide sequence selected from the group consisting of SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13 and SEQ ID NO: 14, the term "comprising" is open-ended. It expands the claimed cyclic peptide to include additional amino acid residues at either or both ends. There is insufficient guidance and working examples that after addition of undisclosed amino acid, the resulting cyclic peptide would maintain both structure and function as the claimed cyclic peptide consisting of the SEQ ID NOS mentioned above. Given the indefinite number of undisclosed amino acids that can be added to said cyclic peptide, it is unpredictable which undisclosed cyclic peptide would be useful for inhibiting the VEGF induced VEGFR-2 and VEGFR-3 mediated cell survival even in vitro.

With regard to claim 18, there is insufficient guidance and working that *any* cyclic peptide produced by the method of Claim 10 would interfere with *any* activity of at least one factor such as VEGF, VEGF-C, VEGF-D mediated at least one receptor such as VEGFR-2 and VEGFR-3. The specification discloses that deletion mutant selected from the group consisting of SEQ ID NO: 10, 11 and 12 having one or two internal amino acid deletion or amino acid substitution **fail to inhibit** the VEGF-DΔNΔC, VEGF-C, VEGF-D and mouse VEGF164 induced VEGFR-2 and/or VEGFR-3 mediated cell survival in vitro. The claim as written is inconsistent with the data provided in the specification.

For these reasons, it would require undue experimentation for one even skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

11. Claims 1-3, 12-13, 18, 23-24, 26, 49-55 and 63 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) *any* monomeric monocyclic peptide which interferes with *any* biological activity of at least one factor selected from the group consisting of VEGF, VEGF-C, and VEGF-D mediated by at least one receptor selected from the group consisting of VEGF receptor-2 and VEGF receptor-3, (2) *any* monomeric monocyclic peptide mentioned above which interferes with *any* biological activity of at least one factor selected from the group consisting of VEGF, VEGF-C, and VEGF-D mediated by at least one receptor selected from the group consisting of VEGF receptor-2, (3) *any* monomeric monocyclic peptide mentioned above which interferes with *any* biological activity of at least one factor selected from the group consisting of VEGF, VEGF-C, and VEGF-D mediated by at least one receptor selected from the group consisting of VEGF receptor-3, (4) *any* monomeric monocyclic peptide produced by *any* method of making a monomeric monocyclic peptide as recited in claim 5, (5) *any* monomeric monocyclic peptide produced by *any* method of making a monomeric monocyclic peptide as recited in claim 5 which interferes with *any* biological activity of at least one factor selected from the group consisting of VEGF, VEGF-C, and VEGF-D mediated by at least one receptor selected from the group consisting of VEGF receptor-2 and VEGF receptor-3, (6) *any* cyclic peptide produced according to the method mentioned above further comprising deleting *any* one or two internal amino acid residues from said loop fragment prior to cyclizing the peptide, (7) *any* composition of matter comprising *any* monomeric monocyclic peptide mentioned above and at least one pharmaceutical carrier or adjuvant, (8) *any* composition of matter comprising *any* monomeric peptide produced by the method mentioned above and at least one pharmaceutical carrier or adjuvant, (9) *any* composition

of matter comprising *any* monomeric monocyclic peptide mentioned above further comprising deleting *any* one or two internal amino acid residues from said loop fragment prior to cyclizing the peptide, and at least one pharmaceutical carrier or adjuvant, and (10) *any* cyclic peptide "comprising" a peptide sequence such as the ones recited in claim 49, wherein the peptide is a monomeric monocyclic peptide which interferes with any biological activity mediated by at least one receptor selected from the group consisting of VEGF receptor-2, VEGRF receptor-3, (11) *any* cyclic peptide comprising SEQ ID NO: 5, SEQ ID NO: 6, (12) *any* cyclic peptide mentioned above which interferes the activity of VEGF-D and/or VEGF-C but not VEGF, mediated by VEGF receptor-2 for treating *any* disease.

The specification discloses only various monomeric monocyclic peptides such as the ones shown in Table 1 on page 32 and Table 2 on page 47 of the specification. However, only three monocyclic peptides (peptides number 1-3), which correspond to SEQ ID NO: 5, 6, 7, respectively, have been demonstrated to inhibit VEGF-DΔNΔC, VEGF-C, VEGF-D and mouse VEGF164 induced VEGFR-2 and VEGFR-3 mediated cell survival in vitro. Note, none of the monocyclic peptides shown in Table 2 and dimeric bicyclic peptides shown in Table 3 were found to inhibit any VEGF, VEGF-DΔNΔC, VEGF-C, VEGF-D and mouse VEGF164 induced VEGFR-2 and VEGFR-3 mediated cell survival in vitro. The specification further discloses that heterodimeric bicyclic peptide number 5, which corresponds to SEQ ID NO: 8 linked to SEQ ID NO: 9 (Table 1 on page 32) caused a significant reduction in number (Fig 11b). In contrast, neither homodimeric bicyclic peptides 4 and 6, which correspond to SEQ ID NO: 8 linked to SEQ ID NO: 8 or SEQ ID NO: 9 linked to SEQ ID NO: 9 caused a significant change in cell number (page 39). None of the dimeric bicyclic peptides mentioned above appear to be more effective inhibitors than the monomeric monocyclic peptides in VEGF-D induced VEGFR-3 cell survival. The specification also discloses that deletion mutant selected from the group consisting of SEQ ID NO: 10, 11 and 12 having one or two internal amino acid deletion or amino acid substitution fail to inhibit the VEGF-DΔNΔC, VEGF-C, VEGF-D and mouse VEGF164 induced VEGFR-2 and VEGFR-3 mediated cell survival in vitro.

With the exception of the specific monomeric monocyclic peptides mentioned above, there is insufficient written description about the structure associated with function of *any* "monomeric monocyclic peptide", *any* cyclic peptide "comprising" *any* SEQ ID NO mentioned above, and *any* composition comprising said "monomeric monocyclic peptide" or "cyclic peptide". Further, the term "comprising" is open-ended. It expands the claimed cyclic peptide to

include additional amino acid residues at either or both ends. There is insufficient written description about the structure associated with function of *any* cyclic peptide "comprising" *any* SEQ ID NO mentioned above. Given that there are only three monomeric monocyclic peptides selected from the group consisting of SEQ ID NO: 5, 6 and 7 have been demonstrated to be effective inhibitors for VEGF induced VEGFR-2 and VEGFR-3 mediated cell survival, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 1-3, 12-13, 18, 23-24, 26 and 63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stacker *et al* (J Biol Chem 274(45): 32127-26; Nov 1999; PTO 892) in view of Potgens *et al* (J Biol Chem 269(52): 32879-85, Dec 1994; PTO 892).

Stacker *et al* teach a monomeric monocyclic compound such as secreted VHD (which is the same as VEGF), VEGF-D and VEGF-DΔNΔC (See page 32123, Fig 4B) that bind to VEGF receptor-2 and/or receptor-3 (See entire document, page 32127, column 2, in particular).

The claimed invention as recited in claim 1 differs from the reference only by the recitation that the monomeric monocyclic peptide which interferences with a biological activity of at least one factor such as VEGF, VEGF-D mediated by at least one receptor selected from the group consisting of VEGF receptor-2 and VEGF receptor-3.

The claimed invention as recited in claim 2 differs from the reference only by the recitation that the monomeric monocyclic peptide which interferences with a biological activity of VEGF-D mediated by VEGF receptor-2.

The claimed invention as recited in claim 3 differs from the reference only by the recitation that the monomeric monocyclic peptide which interferences with a biological activity of VEGF-C or VEGF-D mediated by VEGF receptor-3.

The claimed invention as recited in claim 12 differs from the reference only by the recitation that a monomeric, monocyclic peptide produced by the process of claim 5.

The claimed invention as recited in claim 13 differs from the reference only by the recitation that a monomeric, monocyclic peptide produced by the process of claim 5 which interferences with a biological activity of at least one factor such as VEGF, VEGF-D mediated by at least one receptor selected from the group consisting of VEGF receptor-2 and VEGF receptor-3.

The claimed invention as recited in claim 18 differs from the reference only by the recitation that a cyclic peptide produced according to the method of claim 10 which interferences with a biological activity of at least one factor such as VEGF, VEGF-D mediated by at least one receptor selected from the group consisting of VEGF receptor-2 and VEGF receptor-3.

The claimed invention as recited in claim 23 differs from the reference only by the recitation that a composition of matter comprising a monomeric monocyclic peptide and at least one pharmaceutical carrier or adjuvant.

The claimed invention as recited in claim 24 differs from the reference only by the recitation that a composition of matter comprising a monomeric monocyclic peptide and at least one pharmaceutical carrier or adjuvant.

The claimed invention as recited in claim 26 differs from the reference only by the recitation that a composition of matter comprising a cyclic peptide and at least one pharmaceutical carrier or adjuvant.

The claimed invention as recited in claim 63 differs from the reference only by the recitation that a cyclic peptide, which interferes with the activity of VEGF-D and/or VEGF-C, but not VEGF, mediated by VEGF receptor-2.

Potgens *et al* teach all 8 cysteines in VEGF (VPF) are conserved in PDGF (See page 32880, Fig 1, in particular) and Cys residues are involved in the formation of disulfide bridge that form a cyclic ring structure such as monomer or dimer. Potgens *et al* teach VEGF mutants lacking Cysteine 2, or 4 fails to dimerize (become monomeric) and barely active in inducing endothelial cell proliferation, which is one of the biological activity mediated by VEGF receptors. Potgens *et al* teach the reference monomeric monocyclic peptide having cysteine mutated to the serine at position 2, 4 or 5 were capable of interfering with the biological activity of wild type VEGF. Potgens *et al* teach a composition comprising the reference peptide in PBS, which is a pharmaceutical carrier (See page 32880, column 2, last paragraph, in particular). Potgens *et al* teach VEGF mutant could act as a receptor antagonist that should bind efficiently to the VEGF receptors without activating the receptor and might be of clinical importance in tumor angiogenesis (See page 32884, column 2, third paragraph, in particular).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to substitute the cysteine residues as taught by Potgens *et al* in any VEGF such as VEGF-C and VEGF-D as taught by Stacker *et al* for a monomeric monocyclic peptide which interfere with a biological activity of any VEGF-C or VEGF-D mediated by at least VEGFR-2 and VEGFR-3 as taught by the Potgens *et al* and Stacker *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Potgens *et al* teach VEGF mutant could act as a receptor antagonist that should bind efficiently to the VEGF receptors without activating the receptor and might be of clinical importance in tumor angiogenesis (See page 32884, column 2, third paragraph, in particular). Claims 12-13 and 18 are included in this rejection because a product is a product irrespective of how it is made.

15. No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

17. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Phuong N. Huynh, Ph.D.
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July 1, 2002

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